

Issues in Randomized Clinical Trials Involving Behavioral Interventions

“Randomization”

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Outline

Randomization

- **Key methodologic design feature**
- **Intention to treat principle**
- **How to do the scheme**
- **How to administer**

Some Clinical Trial References:

- Moher D. et al, The CONSORT Statement: Revised Recommendations for Improving the Quality of Reports of Parallel-Group Randomized Trials. *JAMA* 2001;285:1987-1991
- ICH Topic E 9: Statistical Principles for Clinical Trials. The European Agency for the Evaluation of Medicinal Products. *Human Medicines Evaluation Unit* London, March 1998
- Diabetes Care paper: Pan et al, Effects of Diet and Exercise in Preventing NIDDM in People With Impaired Glucose Tolerance: The Da Quing IGT and Diabetes Study. *Diabetes Care* 1997;20(4):537-544

Why Randomize?

- Best way to assure comparability
- In the long run balance of factors
 - Known
 - Unknown
- Statistical hypothesis test based on random assignment
- Selection is impartial: “dice not trying to prove a point” Must convince others of validity of comparison
- Can't predict treatment assignment

Randomization

FIXED ALLOCATION: Assigns with pre-specified probability (not necessarily, though usually, equal)

ADAPTIVE: Changes probabilities during study

Baseline adaptive: - on basis of number per group
- on basis of patient characteristics

Responsive adaptive: - depends on prior outcome

Assumes - rapid response
- stable population source

Probably not appropriate for behavioral trials

Internal Validity

compare treatments

External Validity/ Generalizability

extrapolate to other patients, people

Not realistic to find a random sample of patients for recruitment (at the very least they have to consent)

More important to establish efficacy of treatment before deciding if it can be broadly applied

Randomization assures internal validity

A Classification of Trials

Explanatory (efficacy) - acquire information on the true treatment effects

Pragmatic (management, effectiveness) - make a decision about therapeutic behavioral strategy after taking into account “cost” (withdrawals, side effects) of administering treatment

most closely resembles clinical scenario

treatment policy

treatment intention

Intention to Treat Principle

Intention to treat analysis based on random assignment

“Once randomized - always analyzed”

- entrance criteria

- treatment actually received

 - “crossovers”

- withdrawal from treatment

- deviation from protocol

- adherence to intervention

Should We Only Do One Analysis?

Intention-to-treat primary espoused by FDA and NIH

Secondary analysis

Efficacy subset analysis

Are the results similar? Try to reconcile

Compare baseline characteristics of adherers
versus non-adherers

Can show not comparable but can't prove
they are comparable

Make various assumptions for missing outcome data

Last observation carried forward

Worst case scenario

Practical Issues

Minimize lost to follow-up

Even if poor or no adherence, follow patients

“Fire the statistician if doing so frees enough resources to allow completed data to be obtained. Complete data worth innumerable statistical models to adjust for ignorance”

- Patrick Shrout

How To Do The Randomization Scheme

Simple randomization

Biased coin, urn models

Example:

- Start with 2 balls, one black and one white

- Draw-replace and add one of opposite color

- Prevents imbalance with high probability early on

Random permuted block

- Balance at the end of block

Examples of Blocks for Two Treatments

Size 4

$$\binom{4}{2} = \frac{4!}{2!2!} = \frac{4 * 3 * 2 * 1}{2 * 1 * 2 * 1} = 6$$

1) 1100

2) 1010

3) 1001

4) 0110

5) 0101

6) 0011

Size 6

$$\binom{6}{3} = \frac{6!}{3!3!} = \frac{6 * 5 * 4 * 3 * 2 * 1}{3 * 2 * 1 * 3 * 2 * 1} = 20$$

1) 111000

2) 110100

3) 110010

4) 110001

Etc.

How To Use Blocks When Treatment Is Not Masked

Could predict with unmasked trial – behavior trials can't mask participants or interventionists

Choose the block sizes at random, too

Example: 2 treatments, equal allocation

Block sizes 4, 6, and 8 – random order

Balance in each block

Should You Stratify?

Factors:

Clinical sites in multicenter trial – generally yes

Prognostic variables – generally not necessary

Issues:

Size

Practical considerations

Often governed by custom rather than statistical justification

Stratified ANALYSIS is usually preferred

Minimization

Advantages:

- Balance several prognostic factors
- Balance marginal treatment totals
- Good for small trials (<100 patients)
- Computer makes this fairly easily

Disadvantages:

- Can't prepare treatment assignment
Scheme in advance
- Need up-to-date record
- Not really random - could predict but can introduce random element

Table 5.7. - Treatment Assignments by the Four patient Factors for 80 Patients in an advanced Breast Cancer Trial

Factor	Level	No. on each treatment		Next patient
		A	B	
Performance status	Ambulatory	30	31	←
	Non-ambulatory	10	9	
Age	<50	18	17	←
	≥50	22	23	
Disease-free interval	<2 years	31	32	←
	≥2 years	9	8	
Dominant metastatic lesion	Visceral	19	21	←
	Osseous	8	7	
	Soft tissue	13	12	

Thus, for A this sum = $30 + 18 + 9 + 19 = 76$
while for B this sum = $31 + 17 + 8 + 21 = 77$

Pocock S. *Clinical Trials: A Practical Approach*. John Wiley & Sons, Chichester, England, 1991, p. 85.

Practical Steps in the Randomization of a Patient

Check eligibility

Check informed consent

Formal identification (Trial ID)

RANDOMIZE

Confirmation of patient entry

Tell participant (behavioral trials not masked)

How Random Treatment Assignments Are Administered

Model: Slips in a hat or flipping a coin but should no longer be used in practice

Masked drugs numbered and given in order:
pharmacy, drug manufacturer

But for unmasked trials:

- Envelopes

- Telephone to central unit

 - real person

 - computer

- Microcomputer at the site

 - local

 - central computer

Masked Evaluation of Endpoint

- Behavioral interventions can't be masked: patients or those delivering intervention.
- Can evaluator be masked? Strong design feature.

Examples: Measure of blood pressure, pain scale.

Group Randomization

Intervention targeted at:
physician practices
clinics
community

Randomization works the same way but implications for:

1. selection of endpoint
2. sample size
3. analysis

Diabetes Prevention Study in China

Intervention: diet, exercise, diet plus exercise, control group

Group randomization – clinics – within a clinic all participants got same intervention

**Endpoint: rate of development of diabetes
clinic is unit of analysis**

Secondary analysis – participant as unit of analysis